SCIENTIFIC ARTICLE

Potential Link between Ossification of Nuchal Ligament and the Risk of Cervical Ossification of Posterior Longitudinal Ligament: Evidence and Clinical Implication from a Meta-Analysis of 8429 Participants

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Objective: The aim of the present paper was to evaluate the strength and the magnitude of the association between ossification of the nuchal ligament (ONL) and the risk of cervical ossification of the posterior longitudinal ligament (COPLL) and to determine whether there is a direct association or whether COPLL is a consequence of shared risk factors.

Methods: Medline, Web of Science, Cochrane Library, and Embase databases were searched for studies evaluating the association of COPLL-ONL published before July 2020. Eligible studies were selected based on certain inclusion and exclusion criteria. Two investigators independently conducted the quality assessment and extracted the data, including study designs, countries, patients' age, gender, body mass index (BMI), and the risk of COPLL between individuals with and without ONL. A meta-analysis of homogenous data, a sensitivity analysis, a publication bias assessment, and a subgroup analysis were performed using Stata 12.0 software.

Results: A total of 10 cohort studies involving 8429 participants were incorporated into this analysis. Pooled results demonstrated a statistically significant association between the presence of ONL and the increased COPLL risk (odds ratio [OR] 3.84; 95% confidence interval [CI] 2.68–5.52, $P < 0.001$). Furthermore, subgroup analyses indicated that this association was independent of study design (6.36-fold in case-control studies vs 3.22-fold in cross-sectional studies), sex (6.33-fold in male–female ratio >2.5 vs 2.91-fold in male–female ratio <2.5), age (4.28-fold in age ≥55 years vs 3.45-fold in age <55 years), and BMI (3.88-fold in BMI ≥ 25 kg/m^2 vs 2.43-fold in BMI < 25 kg/m^2), which also indicated that obese, older male patients with ONL had a higher risk of OPLL. Moreover, combined two articles revealed that patients with larger-type ONL had a significantly higher risk of long-segment COPLL compared with controls (OR 1.86; 95% CI 1.41–2.47, $P < 0.001$).

Conclusion: This is the first meta-analysis to demonstrate a strong and steady association between ONL and higher risk of COPLL. This association was independent of sex, age, and BMI. Considering that ONL is generally asymptomatic and easily detectable on X-ray, our findings implied that ONL might serve as an early warning sign of the onset of COPLL and provide clinicians an opportunity for early detection and early intervention.

Key words: Cervical; Meta-analysis; Ossification of the nuchal ligament; Ossification of the posterior longitudinal ligament; Risk

Introduction

Ossification of the posterior longitudinal ligament (OPLL) is defined as a condition of heterotopic ossification of spinal ligaments that occurs more frequently in Asians, especially in Japan[1–4]. OPLL mostly involves the cervical spine, followed by the thoracic and lumbar spine, and it predominantly occurs in males[5, 6]. OPLL is one of the major causes of cervical spinal stenosis and neurological deficits, such as cervical myelopathy and radiculopathy[1, 7–9]. The initiation and progression of OPLL are related to various factors, including familial inheritance, mechanical stress, inflammatory factors, age, diet, and metabolic disorders [6, 8, 10, 11]. However, the underlying pathogenesis of OPLL remains ambiguous. Clinically, OPLL has an insidious onset and progressive course, and occurs in combination with other spinal disorders, which contributes to delayed diagnosis and treatment. To date, surgical intervention is the only effective treatment for symptomatic cervical OPLL (COPLL) that does not respond to conservative management[12, 13]. Therefore, it is of vital importance to predict and detect the risk of COPLL early if a reliable and practical method exists.

Ossification of the nuchal ligament (ONL) is a kind of ossification in the soft tissue posterior to the spinous process of the cervical spine, which is usually asymptomatic and observed accidentally on lateral cervical X-ray[14–16]. The incidence of ONL varies geographically, which is higher in Asians, such as Japanese (10.2% – 27.6%) and Koreans (11.3%), whereas lower in Western populations, such as Americans (6.1%) and Germans (4.5%)[17, 18]. The exact pathogenesis of this ossification is unknown, but chronic trauma, aging and overload, and systemic disorders are assumed to be associated with the onset of ONL[14–16, 19].

Many authors have proposed that ONL might worsen the cervical stability and contribute to other cervical degenerative diseases[16, 17, 20]. In a previous study, cervical spondylosis (83.9%), degenerative disc diseases (80.6%), and osteophyte formation (54.8%) were found in all patients with ONL[16]. Therefore, ONL may act as a comorbidity or a risk factor for other cervical degenerative diseases[16, 21]. Meanwhile, some researchers have speculated that ONL may be one of the spinal ligament ossification syndromes, including OPLL, ossification of the ligamentum flavum, and OALL, which may exert important influence in the initiation and progression of these conditions[22–24]. Because of OPLL being most common in the cervical spine, it is worth studying whether the existence of ONL is associated with the appearance and extent of COPLL. Fujimori et al.[25] found that patients with ONL were more likely to have COPLL than those without ONL (7.2% vs 1.6%, odds ratio [OR] = 4.8, $P < 0.001$). Kim et al.[26] demonstrated that the prevalence of COPLL was almost 2.5 times greater in patients with ONL than those without ONL, and the morphology of ONL was related to the degree of COPLL involved. Another recent study discovered that the presence of ONL was associated with increased risk of COPLL ($P = 0.037$), but the length of COPLL and ONL had no correlation ($P = 0.233$)[27].

Despite the accumulation of recent studies supporting the COPLL-ONL correlation, there is no specialized meta-analysis that quantitatively assesses the association between ONL and the risk of COPLL. Thus, we conducted this systematic review and meta-analysis aiming to: (i) investigate whether there is a potential association between the ONL and the risk of COPLL in terms of incidence or extent; (ii) determine the strength and magnitude of this association; (iii) explore whether ONL is associated with COPLL as a consequence of shared risk factors or whether ONL contributes to COPLL in an independent fashion through stratified analyses.

Materials and Methods

Inclusion and Exclusion Criteria

Studies included met the following inclusion criteria: (i) participant: patients diagnosed with ONL;
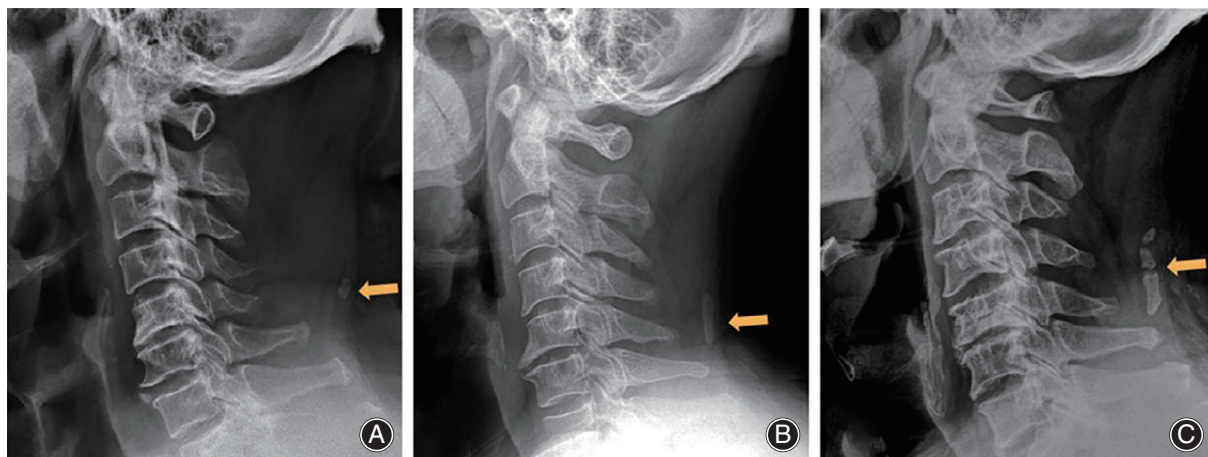

Fig. 1 Classification of ossification of the nuchal ligament in cervical lateral radiographic images. (A) Round type. (B) Rod type. (C) Segmented type.
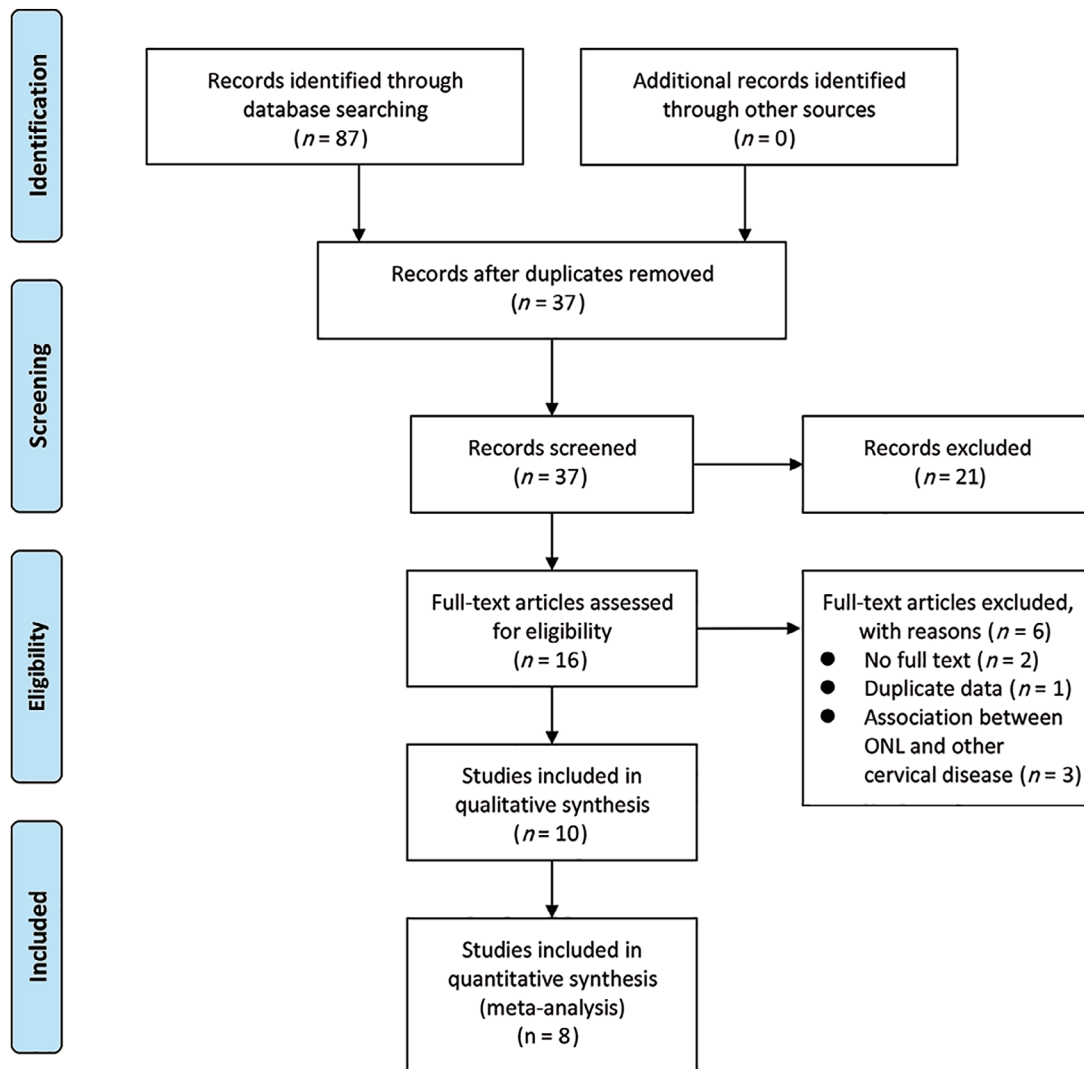
Fig. 2 Flow diagram of the study identification and selection process. ONL, ossification of the nuchal ligament.

TABLE 1 Characteristics of the studies investigating the relationship between ONL and COPLL prevalence

First author, year	Country	Study period	Study design	Sample size (M/F)	Mean age (years)	ONL+ OPLL+	ONL+ OPLL-	ONL- OPLL+	ONL- OPLL-
Wang et al., 2014[31]	China	2010–2013	CS	372 (268/104)	54.4 (27–81)	42	143	8	179
Takahito et al., 2015[25]	USA	2009–2012	CS	3161 (2089/1072)	51.2 ± 21.6	25	321	45	2770
Duk et al., 2015[23]	Korea	2008–2014	CC	210 (162/48)	56.9 (39–77)	68	37	17	88
Kim et al., 2016[26]	Korea	2010–2015	CC	248 (196/52)	57.8 (38–79)	70	54	28	96
Takahito et al., 2016[32]	Japan	2006–2013	CS	1500 (888/612)	57.0 (21–94)	43	302	52	1103
Myung et al., 2019[27]	Korea	2005–2015	CS	297 (206/91)	51.0 (13–93)	10	64	13	210
Liang et al., 2019[35]	China	2010–2013	CS	2000 (1335/65)	48.5 (22–95)	38	592	44	1326
Ying et al., 2019[36]	China	2015–2016	CS	191 (124/67)	58.1	29	44	22	96

CC, control-case; CS, cross-sectional; COPLL, cervical ossification of the posterior longitudinal ligament; M/F, male/female; ONL, ossification of the nuchal ligament; OPLL, ossification of the posterior longitudinal ligament.

TABLE 2 Characteristics of the Studies investigating the relationship between ONL and the extent of COPLL

First author, Year	Country	Study period	Study design	Sample size (M/F)	Mean age (years)	ONL morphology measures	OPLL extent measures
Duk et al., 2015[23]	Korea	2008-2014	CC	210 (162/48)	56.9 (39–77)	The types of OLN (round type; rod and segmented type)	The number of involved OPLL level (short-level OPLL, 1–3 levels; long-level OPLL, 4–6 levels)
Kim et al., 2016[26]	Korea	2010–2015	CC	248 (196/52)	57.8 (38–79)	The types of OLN (round type; rod and segmented type)	The number of involved OPLL level (short-level OPLL, 1–3 levels; long-level OPLL, 4–6 levels)
Myung et al., 2019[27]	Korea	2005–2015	CS	297 (206/91)	51.0 (13–93)	The length from the superior end to the inferior end of ONL	The length from the superior end to the inferior end of OPLL
Yuan et al., 2018[33]	China	2010–2016	CS	217 (156/61)	56.4 (36–81)	The location of ONL determined by the horizontal midline of the vertebra	The level of which the spinal canal occupation ratio (COR) of OPLL
Yoshii et al., 2019[34]	Japan	NA	CS	233 (177/56)	65.3 (33–93)	The presence of ONL	OP-index defined as the sum of the level of ossification at the vertebral bodies and the intervertebral discs

CC, control-case; COPLL, cervical ossification of the posterior longitudinal ligament; CS, cross-sectional; M/F, male/female; NA, not available; ONL, ossification of the nuchal ligament; OPLL, ossification of the posterior longitudinal ligament.

(ii) intervention: the number of ONL patients; (iii) comparison: the number of non-ONL patients; (iv) outcomes: the risk of COPLL patients between ONL and non-ONL patients; and (v) study design: observational studies including the cross-sectional, case-control, or cohort study.

Studies were excluded according to the following exclusion criteria: (i) animal model or *in vitro* studies; (ii) reviews, case reports, letters, and comments; (iii) the data from studies was obviously paradoxical or not presented clearly enough; and (iv) duplicate reports.

Data Sources and Search Strategy

The meta-analysis was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[28]. Electronic literature searches with no language restrictions were performed independently by two researchers (Baoliang Zhang and Guanghui Chen) *via* the Medline, Web of Science, Embase, and Cochrane databases, from the inception to July 2020, using a combination of search terms in medical subject headings (MeSH): "ossification of the posterior longitudinal ligament" and "ossification of the nuchal ligament." A third independent investigator (Xingshuai Gao) resolved any disagreement. Furthermore, references and citations of the retrieved articles were screened to identify further relevant articles. The assessment involved three stages: screening of titles, abstracts, and full texts.

Data Extraction

The following information was extracted from the included studies by two reviewers independently (Baoliang Zhang and Guanghui Chen): first author, publication year, country, study period, study design, sample size, sources of patients, sex, mean age, number of subjects in cases and controls, and potential confounders. Discrepancies in data extraction were resolved through consultation with the third reviewer (Xingshuai Gao).

Quality Assessment

The methodological quality of studies included was assessed using the Newcastle–Ottawa Scale (NOS)[29]. The practicable questions from the NOS for case-control studies were applied to assess the cross-sectional studies due to the lack of a validated method. Criteria for qualitative assessment comprised three main items: sample selection, comparability, and exposure. Each of these items had questions with options and could receive 1 or 2 points if the criteria were achieved. In the analysis, studies with NOS scores of 1–3, 4–6, and 7–9 were defined as of low, moderate, and high quality, respectively. The studies assessed by both investigators (Baoliang Zhang and Guanghui Chen) were compared, and disagreements were resolved by consensus.

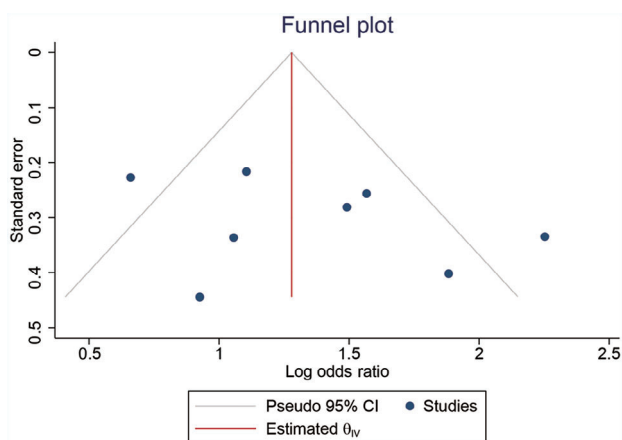| TABLE 3 Methodologic quality assessment of included studies				
Studies	Selection	Comparability	Outcome/Exposure	Total
Wang et al.[31]	3	1	3	7
Takahito et al.[25]	3	0	2	5
Duk et al.[23]	3	2	3	8
Kim et al.[26]	3	2	3	8
Takahito et al.[32]	3	0	2	5
Yuan et al.[33]	3	0	3	6
Myung et al.[27]	3	1	3	7
Liang et al.[34]	3	1	3	6
Ying et al.[35]	2	0	3	5
Yoshii et al.[36]	3	0	3	6

Fig. 3 Funnel plot for testing the publication bias of the association between ossification of the nuchal ligament and the risk of cervical ossification of the posterior longitudinal ligament. Each point represents an individual study on the indicated association. The vertical line indicates the effect size. CI, confidence interval.

Diagnosis and Morphological Classification of Ossification of the Nuchal Ligament

Ossification of the nuchal ligament was diagnosed through cervical X-ray, and was divided into round, rod, and segmented types according to the morphologic patterns of ossification (Fig. 1)[23]. When the longest axis of an ONL was less than 10 mm in the sagittal plane, it was classified as round; when exceeding 10 mm in the sagittal plane, it was classified as a rod type ONL if continuous or a segmented type ONL if discontinuous[23]. To allow for comparison with round type, rod and segmented type were defined as larger type.

Diagnosis and Classification of Extent of Ossification of the Posterior Longitudinal Ligament

Cervical OPLL was diagnosed with cervical CT. As for the extent of COPLL, the common assessment criteria were applied in 2 studies: there was a short-level (1–3 levels) OPLL group and a long-level (4–6 levels) OPLL group based on the number of intervertebral spaces involved by OPLL[23, 26]. Long-level OPLL was considered more severe than short-level OPLL.

Statistical Analysis

We used the pooled OR with a 95% CI to evaluate the relationship between ONL and the risk of OPLL as well as the association between the type of ONL and the severity of OPLL. Sensitivity analysis and subgroup analysis were conducted to determine the robustness of the outcome. The I^2 statistic was used to assess the degree of heterogeneity among studies. The values 25, 50, and 75% corresponded to low, moderate, and high heterogeneity, respectively. A fixed-effect model was applied if $I^2 < 50\%$, and a random-effect model was used if $I^2 > 50\%$[30]. Publication bias was statistically assessed through visual inspection of the funnel plot. All statistical tests were performed using the Stata 12.0 software. P-values less than 0.05 were considered statistically significant.

Results

Search Results

Based on the search strategy, 87 potentially relevant articles were identified from the electronic database. After duplicates were removed, 37 unique abstracts remained. After screening titles and abstracts, 21 irrelevant studies were excluded because they failed to meet the inclusion criteria. A total of 16 studies were subsequently assessed by full-text review, and 6 studies were excluded for the following reasons: no full text ($n = 2$), duplicate data ($n = 1$), and not reporting the association between ONL and OPLL ($n = 3$). Finally, the remaining 10 studies[23, 25–27, 31–36] met our selection criteria and were included in the review. The detailed search strategy through the PRISMA flow diagram is presented in Fig. 2.

Study Characteristics

All studies, involving 8429 participants with eight cross-sectional designs[25, 27, 31–36] and two case-control designs[23, 26] were published between 2014 and 2019. A total of 4 studies[31, 33, 35, 36] were conducted in China, 2 in Japan[32, 34], 3 in Korea[23, 26, 27], and only 1 in the United States[25]. The sample
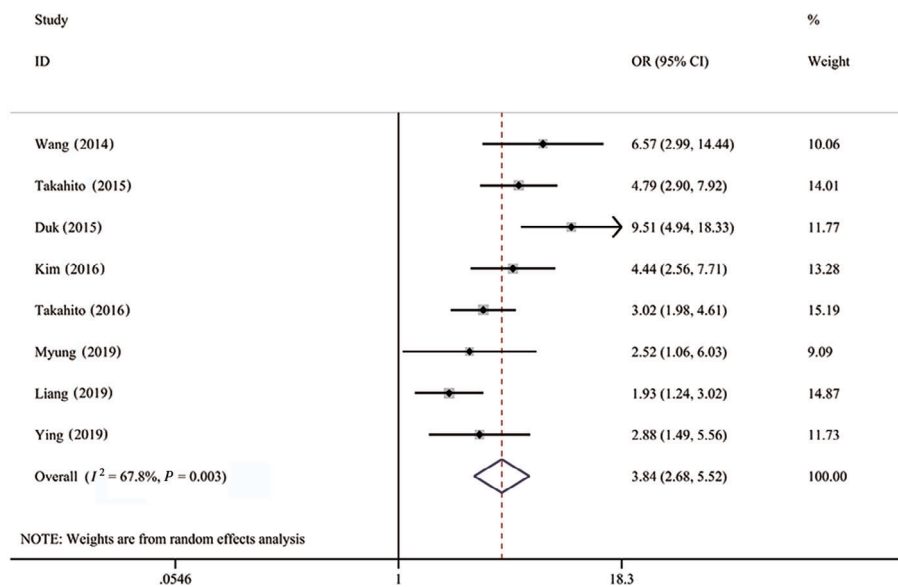
LINK BETWEEN ONL AND THE RISK OF COPLL

Fig. 4 Forest plot of included studies estimating the risk of cervical ossification of the posterior longitudinal ligament and ossification of the nuchal ligament. The diamond represents the pooled odds ratio (OR) and 95% confidence interval (CI).
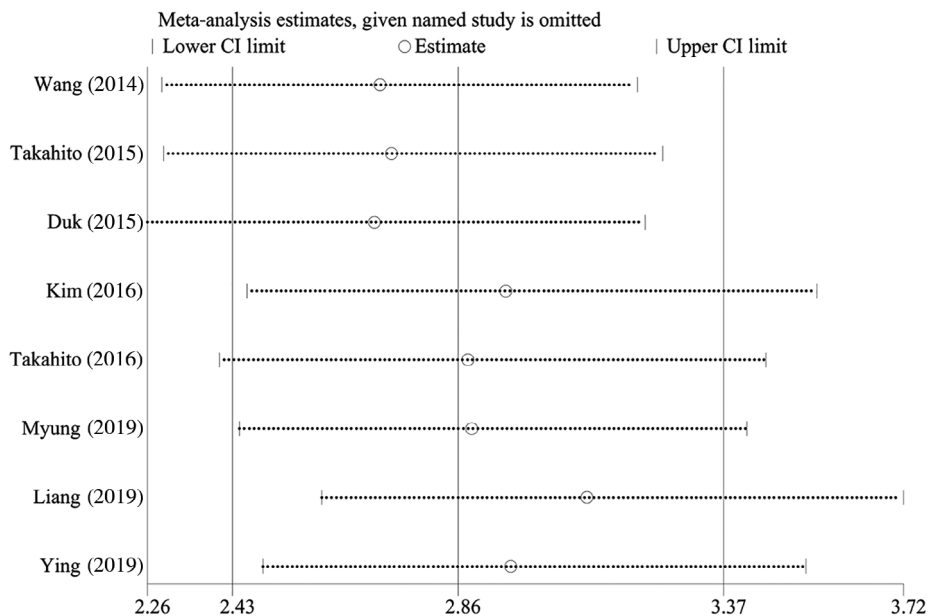

Fig. 5 Sensitivity analysis through excluding 1 study at a time. The middle line represents the pooled effect value. The bilateral lines represent the 95% confidence interval (CI).

size ranged from 191 to 3161 participants. Of these 10 studies, there were 8 reporting the relationship between ONL and the risk of OPLL, including 1882 cases and 6097 controls[23, 25–27, 31, 32, 35, 36]. In addition, there were 5 studies[23, 26, 27, 33, 34] revealing the correlation between presence or types of ONL and the extent of OPLL, only 2 studies[23, 26] of which were available for a pooled analysis due to non-uniform measurement methods of the other 3 articles[27, 33, 34]. Study characteristics are summarized in Table 1 for investigating the relationship between ONL and the risk of COPLL and in Table 2 for ONL and the extent of COPLL.

Quality Assessment and Publication Bias

Two investigators assessed the quality of studies independently. A total of 3 studies[25, 32, 35] scored 5, 3 studies[33, 34, 36] scored 6, 2 studies[27, 31] scored 7, and 2 studies[23, 26] scored 8, with an average NOS score of 6.3, indicating that all studies were of fairly satisfactory quality (Table 3). Given the comparability, many studies did not control potentially confounding factors, which led to the reduced quality. Based on visual inspection of the funnel plots, they appeared basically symmetric, which demonstrated that there was no significant publication bias (Fig. 3).

Fig. 6 Forest plot of remaining studies estimating the risk of cervical ossification of the posterior longitudinal ligament and ossification of the nuchal ligament after a sensitivity analysis. The diamond represents the pooled odds ratio (OR) and 95% confidence interval (CI).
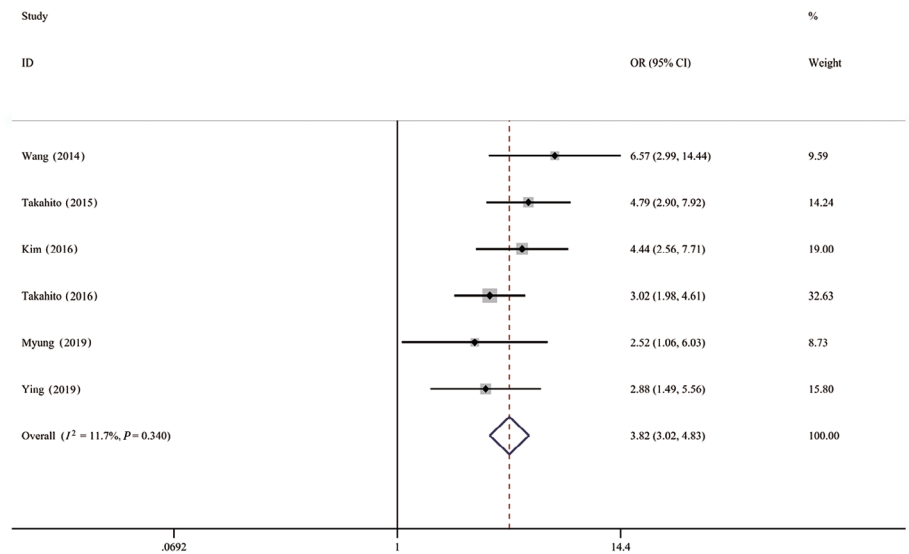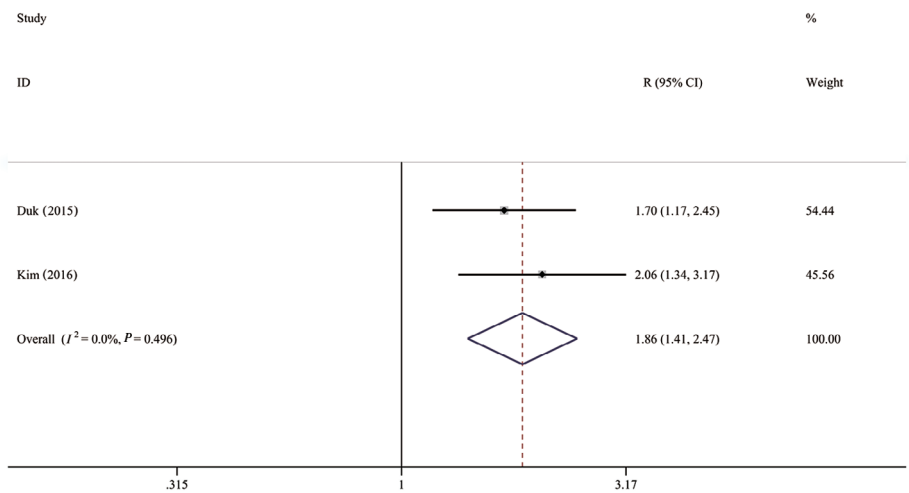

Fig. 7 Forest plot of 2 studies estimating the types of ossification of the nuchal ligament and the length of cervical ossification of the posterior longitudinal ligament. The diamond represents the pooled odds ratio (OR) and 95% confidence interval (CI).

Meta-Analysis and Sensitivity Analysis

Association between the Presence of Ossification of the Nuchal Ligament and the Risk of Ossification of the Posterior Longitudinal Ligament

Eight studies investigated the association between the presence of ONL and the risk of OPLL. Included studies reported that the prevalence of COPLL in ONL patients ranged from 6.0% to 64.7% versus a range of 1.6% to 22.6% in controls. The combined results demonstrated that there was a statistically significant association between the presence of ONL and the risk of COPLL (OR 3.84; 95% CI 2.68–5.52; $P < 0.001$; $I^2 = 67.8\%$; random-effect model) (Fig. 4). Because of high heterogeneity, a sensitivity analysis was performed (Fig. 5). When the studies by Duk et al.[23] and Liang et al.[35] were removed from the analysis, the pooled results did not change substantially (OR 3.82; 95% CI 3.02–4.83; $P < 0.001$; fixed-effect model). However, the heterogeneity was significantly reduced ($I^2 = 11.7\%$, $P = 0.340$) when they were excluded from the meta-analysis (Fig. 6).

Association between the Type of Ossification of the Nuchal Ligament and the Extent of Ossification of the Posterior Longitudinal Ligament

Five studies showed the relationship between the location or types of ONL and the extent of COPLL. However, only 2 studies made use of a consistent evaluation method by detecting the association between morphotypes of ONL and the numbers of involved COPLL levels. Pooling results revealed that the larger type (rod or segmented) of ONL had a higher risk of long-level COPLL than the round type ONL,
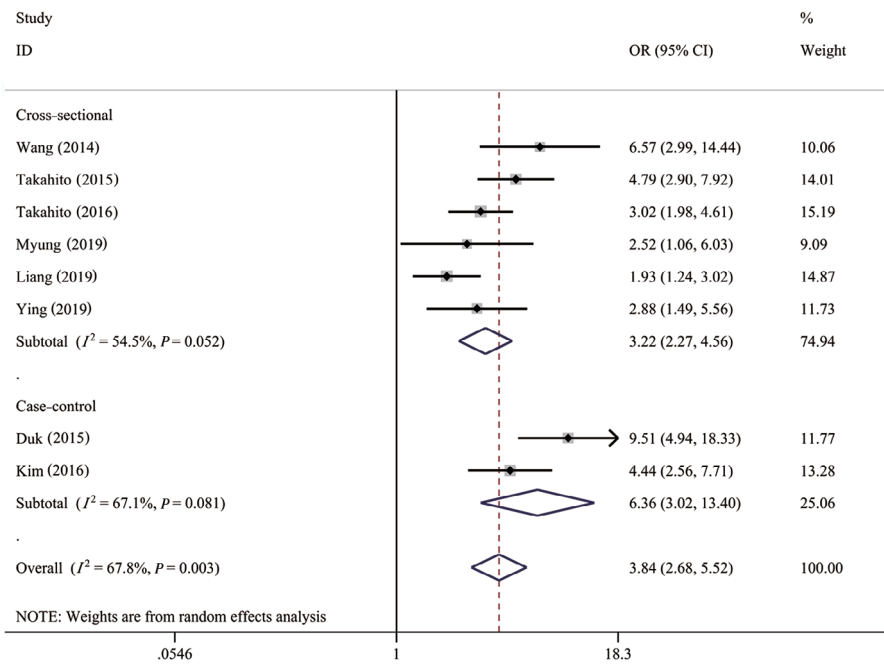
LINK BETWEEN ONL AND THE RISK OF COPLL

Study ID | OR (95% CI) | % Weight

Cross-sectional

Study ID	OR (95% CI)	% Weight
Wang (2014)	6.57 (2.99, 14.44)	10.06
Takahito (2015)	4.79 (2.90, 7.92)	14.01
Takahito (2016)	3.02 (1.98, 4.61)	15.19
Myung (2019)	2.52 (1.06, 6.03)	9.09
Liang (2019)	1.93 (1.24, 3.02)	14.87
Ying (2019)	2.88 (1.49, 5.56)	11.73
Subtotal ($I^2 = 54.5\%$, $P = 0.052$)	3.22 (2.27, 4.56)	74.94

Case-control

Study ID	OR (95% CI)	% Weight
Duk (2015)	9.51 (4.94, 18.33)	11.77
Kim (2016)	4.44 (2.56, 7.71)	13.28
Subtotal ($I^2 = 67.1\%$, $P = 0.081$)	6.36 (3.02, 13.40)	25.06
Overall ($I^2 = 67.8\%$, $P = 0.003$)	3.84 (2.68, 5.52)	100.00

NOTE: Weights are from random effects analysis

.0546   1   18.3

Fig. 8 Subgroup analysis on the association between risk of cervical ossification of the posterior longitudinal ligament and ossification of the nuchal ligament according to study design. CI, confidence interval; OR, odds ratio.
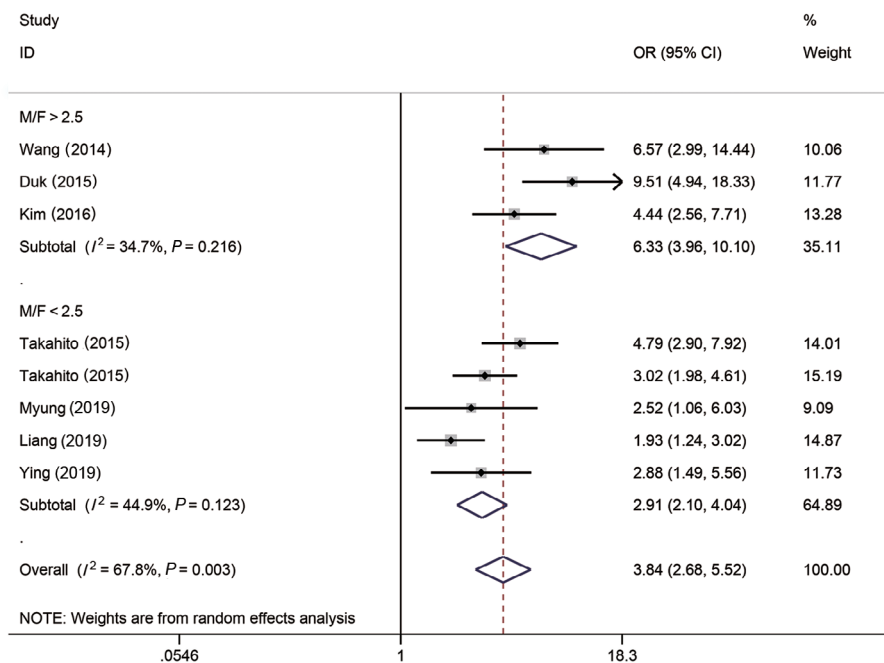
Study ID | OR (95% CI) | % Weight

M/F > 2.5

Study ID	OR (95% CI)	% Weight
Wang (2014)	6.57 (2.99, 14.44)	10.06
Duk (2015)	9.51 (4.94, 18.33)	11.77
Kim (2016)	4.44 (2.56, 7.71)	13.28
Subtotal ($I^2 = 34.7\%$, $P = 0.216$)	6.33 (3.96, 10.10)	35.11

M/F < 2.5

Study ID	OR (95% CI)	% Weight
Takahito (2015)	4.79 (2.90, 7.92)	14.01
Takahito (2015)	3.02 (1.98, 4.61)	15.19
Myung (2019)	2.52 (1.06, 6.03)	9.09
Liang (2019)	1.93 (1.24, 3.02)	14.87
Ying (2019)	2.88 (1.49, 5.56)	11.73
Subtotal ($I^2 = 44.9\%$, $P = 0.123$)	2.91 (2.10, 4.04)	64.89
Overall ($I^2 = 67.8\%$, $P = 0.003$)	3.84 (2.68, 5.52)	100.00

NOTE: Weights are from random effects analysis

.0546   1   18.3

Fig. 9 Subgroup analysis on the association between risk of cervical ossification of the posterior longitudinal ligament and ossification of the nuchal ligament according to male–female ratio. CI, confidence interval; OR, odds ratio.

which was statistically significant (OR 1.86; 95% CI 1.41–2.47; $P < 0.001$; $I^2 = 0.0\%$; fixed-effect model) (Fig. 7).

Subgroup Analysis based on Study Design, Sex, Age, and Body Mass Index
Subgroup analyses were performed to determine whether ONL directly associates with the risk of OPLL or is a consequence of shared risk factors based on study design, sex (male-female ratio), age and body mass index (BMI). In the meantime, these analyses also further explained the heterogeneity.

When stratified by design, this heterogeneity subsided for cross-sectional studies ($I^2 = 54.5\%$) compared to overall heterogeneity ($I^2 = 67.8\%$), while the pooled estimate was
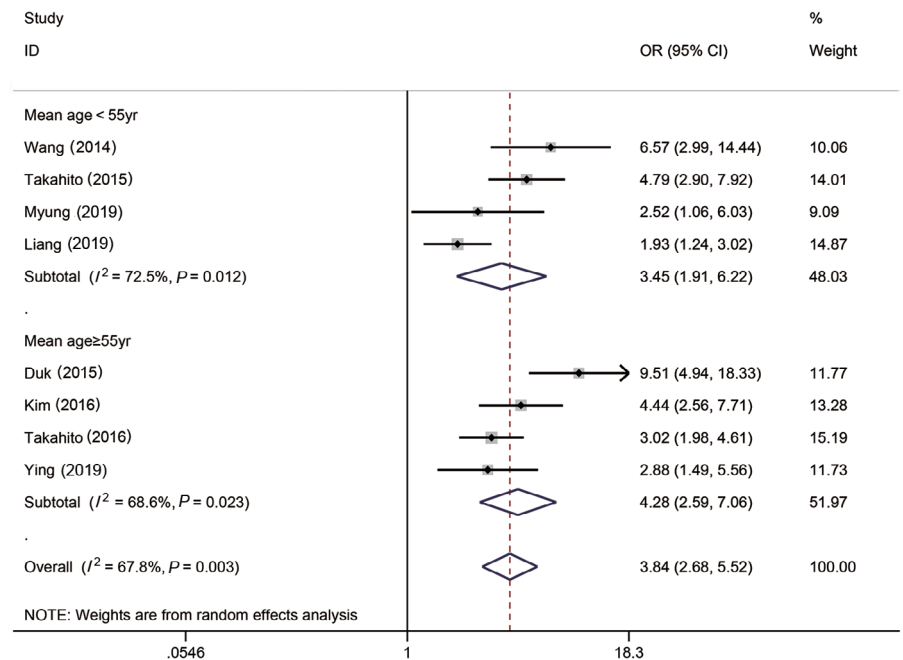
Fig. 10 Subgroup analysis on the association between risk of cervical ossification of the posterior longitudinal ligament and ossification of the nuchal ligament according to age. CI, confidence interval; OR, odds ratio.
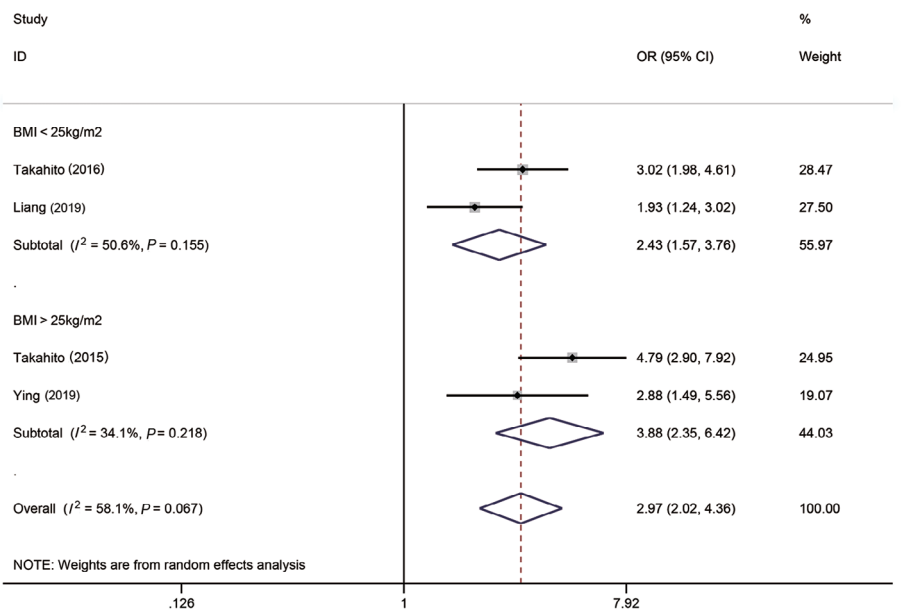

Fig. 11 Subgroup analysis on the association between risk of cervical ossification of the posterior longitudinal ligament and ossification of the nuchal ligament according to body mass index.

not modified meaningfully (OR = 3.22, 95% CI 2.27–4.56; $P < 0.001$). In constrast, in the case-control group, heterogeneity was still large ($I^2 = 67.1\%$) and the pooled result was increased significantly (OR = 6.36, 95% CI 3.02–13.40; $P < 0.001$) (Fig. 8).

According to the male–female ratio, we observed a significant association with a larger magnitude of correlation in groups with male–female ratio >2.5 (OR = 6.33; 95% CI 3.96–10.10; $P < 0.0001$; $I^2 = 34.7\%$) than those with male–female ratio <2.5 (OR = 2.91; 95% CI 2.10–4.04; $P < 0.0001$; $I^2 = 44.9\%$). In addition, low heterogeneity was found in both subgroups (Fig. 9).

When stratified by age, we separated the studies into subgroups with mean age <55 years and mean age ≥55 years. We identified a significantly increased risk for developing ONL-associated COPLL in patients with the mean age
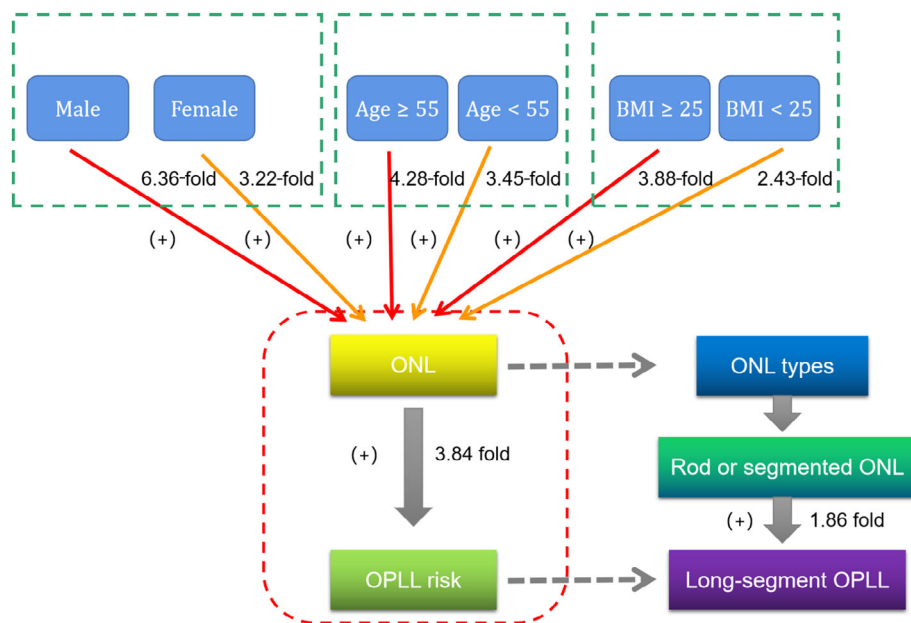
Fig. 12 A schematic illustrative diagram showing the relationship of ossification of the nuchal ligament (ONL) and cervical ossification of the posterior longitudinal ligament (OPLL) and related risk factors.

≥55 years subgroup (OR = 4.28, 95% CI 2.59–7.61; $P < 0.0001$; $I^2 = 68.6\%$) than those with mean age <55 years (OR = 3.45, 95% CI 1.91–6.22; $P < 0.0001$; $I^2 = 72.5\%$). Nevertheless, there was significant heterogeneity in both subgroups (Fig. 10).

Based on BMI, we defined BMI < 25kg/m^2 and BMI ≥ 25 kg/m^2 as non-obese groups and obese groups. We identified a significant association between ONL and the prevalence of COPLL in both subgroups and the OR was 3.88 (95% CI 2.35–6.42; $P < 0.0001$; $I^2 = 34.1\%$) and 2.43 (95% CI 1.57–3.76; $P < 0.0001$; $I^2 = 50.6\%$), respectively. As shown above, low heterogeneity was found in obese groups, while high heterogeneity was found in non-obese groups (Fig. 11).

Taken together, all aforementioned subgroup analysis results further demonstrated that ONL was more likely associated with the increased risk of COPLL, which was independent of study design, sex, age and BMI.

Discussion

Several epidemiological studies have revealed the relationship between ONL and COPLL, but the strength and magnitude of this association and whether ONL is an independent risk factor for initiation and development COPLL remain inconclusive. The exact relationship between ONL and the risk of COPLL requires further elucidation because it may provide clinical guidance for early detection and prevention of insidious and progressive OPLL. To the best of our knowledge, this was the first comprehensive systematic review and meta-analysis based on current evidence determining the relationship between ONL and the risk of COPLL. The meta-analysis results demonstrated that ONL was markedly associated with an increased risk of COPLL,

which was independent of age, gender, and BMI, and this link was robust across sensitivity analyses. Furthermore, we found that patients with larger types of ONL had a higher risk of long-level COPLL.

The underlying mechanisms behind the observed association between ONL and the risk of COPLL remain obscure, but several similarities in the epidemiology and pathogenesis may imply this relationship. First, these two diseases occur mostly in the cervical spine, and the onset of ONL can destroy the cervical stability, which is the leading cause of many cervical degenerative diseases, including COPLL[31, 33]. Substantive evidence revealed that COPLL and ONL often appeared in the same segment, such as in C5–6 and C4–5[31, 33]. Second, the incidence of the two diseases is much higher in Asia than in the West, especially in the Japanese population, in whom there may be a genetic predisposition[16, 25]. Third, their incidence presents a similar gender difference; that is, COPLL and ONL are significantly more common in men than in women[23, 26, 32, 37]; in addition, older patients, in their 50s and 60s, are more susceptible to these two diseases[1, 2, 17, 26, 31, 39]. Finally, COPLL and ONL have some shared risk factors, such as mechanical stimulation, obesity, hormonal imbalance, and systemic diseases (e.g. diabetes mellitus, hyperparathyroidism, hypoparathyroidism, and calcium-phosphorus metabolism disorders)[2, 26, 32, 35, 38–41]. Hence, we speculated that ONL might coexist with COPLL or be a risk factor for COPLL. Recently, emerging studies also demonstrated the possible link between ONL and COPLL. Kim *et al.*[29] reported that the prevalence of COPLL was almost 2.5 times greater in patients with ONL than those without ONL. Duk *et al.*[26] proved the two-way relationship between ONL and COPLL. They found that not only the prevalence of COPLL was significantly higher in the patients with ONL (64.7%) than

without ONL (16.1%) but the COPLL patients (54.2%) were more likely to have ONL than those without COPLL (29.5%). Toshitaka *et al.*[34] demonstrated that the ossification indexes of COPLL were higher in ONL (+) patients than in ONL (−) patients, which revealed that co-existence of ONL might signify a severe predisposition to OPLL.

In this research, the pooled effect estimated from 8 included papers demonstrated a 3.84-fold increased risk of COPLL in ONL patients compared with non-ONL individuals. Nevertheless, substantial heterogeneity was observed. To determine the sources of heterogeneity, a sensitivity analysis was conducted. Heterogeneity was obviously decreased, while the pooled results did not change substantially when excluding the following 2 studies, indicating that the 2 studies were the source of heterogeneity. They were studies by Duk *et al.*[23] and Liang *et al.*[35]. The population source selected by Duk *et al.*[23] was only patients with cervical degenerative disease and the sample size was small, which may be the reason for its heterogeneity. Liang *et al.*[35] did not randomly select the study population, which inevitably created a sample selection bias. Moreover, we found that the rod or segmented types of ONL showed a higher incidence of long-segment COPLL than round type ONL, statistically significantly, which may represent a new direction to predict the severity of COPLL in future. However, having only 2 studies combined might increase the inaccuracy of the conclusion, and previous studies revealed that the extent of COPLL was significantly associated with female sex and obesity[4] rather than the presence of ONL[3].

An issue that should be addressed is whether ONL is associated with COPLL as a consequence of shared risk factors, or whether ONL contributes to COPLL in an independent fashion. Therefore, it was necessary to conduct a further subgroup analysis for potential confounding factors. When stratified by study design, a larger prevalence of COPLL in ONL patients was found in the case-control studies with a higher heterogeneity. The reason might be the limited number of studies and their retrospective nature. Furthermore, other subgroup meta-analyses revealed that the association between ONL and COPLL might be modulated by the age, sex, and BMI but independent of them. Obese, older male patients with ONL had a higher risk of COPLL. Various epidemiological investigations found that the prevalence of COPLL had a conspicuous male predominance of 2:1 to 3:1 and increased with advancing age, characterized as 50 years at onset and 60 years at peak[42–45]. In addition, accumulating studies have demonstrated that COPLL-positive individuals have significantly higher weight, BMI[35, 46], and serum leptin/BMI ratio[47, 48]. In view of hyperleptinemia being a common feature of obese people, leptin played an important role in linking macroscopical manifestations of obesity with molecular mechanisms of COPLL[11, 48]. Therefore, these factors, including the presence of ONL, might function independently. However, regression analyses could not be performed to draw conclusions because of the limited number of studies. All subgroup estimates indicated that ONL was significantly associated with an increased risk of COPLL in an independent fashion.

This study has several limitations. First, there are a limited number of studies evaluating the association of ONL-COPLL, which might influence the robustness of the results, and precluded more subgroup analyses stratified by potential confounding factors. Second, there was significant heterogeneity across studies, but we a performed sensitivity analysis and subgroup analyses to explain the source of the heterogeneity as far as possible. Third, all studies included were observational, which might cause bias due to unmeasured confounders. Finally, because of different assessment standards and measures for the extent of ONL and COPLL, only 2 studies with homologous data were combined to determine the size of ONL and the severity of COPLL, so this result should be interpreted with caution.

Conclusion

In summary, despite some limitations, this meta-analysis proved that ONL was significantly associated with high risk of COPLL, which was independent of sex, age, and BMI. In addition, we also found that people with larger-type ONL were more inclined to long-level COPLL, despite only 2 studies being included. A schematic illustrative diagram was drawn to show the relationship of ONL-COPLL and related risk factors (Fig. 12). Considering that the ONL is innocuous and more easily detectable than OPLL on cervical radiographs, it may provide clinicians a direction to predict the risk of COPLL through ONL. Of course, the detailed mechanisms underlying the relationship between ONL and COPLL need further evaluation in prospective high-quality studies in future.

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